

Alkaloid

Alkaloids are a class of naturally occurring organic compounds that mostly contain basic nitrogen atoms. This group also includes some related compounds with neutral^[2] and even weakly acidic properties.^[3] Some synthetic compounds of similar structure may also be termed alkaloids.^[4] In addition to carbon, hydrogen and nitrogen, alkaloids may also contain oxygen, sulfur and, more rarely, other elements such as chlorine, bromine, and phosphorus.^[5]

Alkaloids are produced by a large variety of organisms including bacteria, fungi, plants, and animals.^[6] They can be purified from crude extracts of these organisms by acid-base extraction, or solvent extractions followed by silica-gel column chromatography.^[7] Alkaloids have a wide range of pharmacological activities including antimalarial (e.g. quinine), antiasthma (e.g. ephedrine), anticancer (e.g. homoharringtonine),^[8] cholinomimetic (e.g. galantamine),^[9] vasodilatory (e.g. vincamine), antiarrhythmic (e.g. quinidine), analgesic (e.g. morphine),^[10] antibacterial (e.g. chelerythrine),^[11] and antihyperglycemic activities (e.g. piperine).^[12] Many have found use in traditional or modern medicine, or as starting points for drug discovery. Other alkaloids possess psychotropic (e.g. psilocin) and stimulant activities (e.g. cocaine, caffeine, nicotine, theobromine),^[13] and have been used in entheogenic rituals or as recreational drugs. Alkaloids can be toxic too (e.g. atropine, tubocurarine).^[14] Although alkaloids act on a diversity of metabolic systems in humans and other animals, they almost uniformly evoke a bitter taste.^[15]

The boundary between alkaloids and other nitrogen-containing natural compounds is not clear-cut.^[16] Compounds like amino acid peptides, proteins, nucleotides, nucleic acid, amines, and antibiotics are usually not called alkaloids.^[2] Natural compounds containing nitrogen in the exocyclic position (mescaline, serotonin, dopamine, etc.) are usually classified as amines rather than as alkaloids.^[17] Some authors, however, consider alkaloids a special case of amines.^{[18][19][20]}



The first individual alkaloid, morphine, was isolated in 1804 from the opium poppy (*Papaver somniferum*).^[1]

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Naming

The name "alkaloids" (German: *Alkaloide*) was introduced in 1819 by the German chemist Carl Friedrich Wilhelm Meißner, and is derived from late Latin root *alkali* (which, in turn, comes from the Arabic *al-qalwī* meaning 'ashes of plants') and the suffix -οειδής -('like').^[nb 1] However, the term came into wide use only after the publication of a review article, by Oscar Jacobsen in the chemical dictionary of Albert Ladenburg in the 1880s.^{[21][22]}

There is no unique method for naming alkaloids.^[23] Many individual names are formed by adding the suffix "ine" to the species or genus name.^[24] For example, atropine is isolated from the plant *Atropa belladonna*; strychnine is obtained from the seed of the Strychnine tree (*Strychnos nux-vomica* L.).^[5] Where several alkaloids are extracted from one plant their names are often distinguished by variations in the suffix: "idine", "anine", "aline", "inine" etc. There are also at least 86 alkaloids whose names contain the root "vin" because they are extracted from vinca plants such as *Vinca rosea* (*Catharanthus roseus*);^[25] these are called vinca alkaloids.^{[26][27][28]}

History



Friedrich Sertürner, the German chemist who first isolated morphine from opium.

Alkaloid-containing plants have been used by humans since ancient times for therapeutic and recreational purposes. For example, medicinal plants have been known in Mesopotamia from about 2000 BC.^[29] The *Odyssey* of Homer referred to a gift given to Helen by the Egyptian queen, a drug bringing oblivion. It is believed that the gift was an opium-containing drug.^[30] A Chinese book on houseplants written in 1st–3rd centuries BC mentioned a medical use of ephedra and opium poppies.^[31] Also, coca leaves have been used by South American Indians since ancient times.^[32]

Extracts from plants containing toxic alkaloids, such as aconitine and tubocurarine, were used since antiquity for poisoning arrows.^[29]

Studies of alkaloids began in the 19th century. In 1804, the German chemist Friedrich Sertürner isolated from opium a "soporific principle" (Latin: *principium somniferum*), which he called "morphium", referring to Morpheus, the Greek god of dreams; in German and some other Central-European languages, this is still the name of the

drug. The term "morphine", used in English and French, was given by the French physicist Joseph Louis Gay-Lussac.

A significant contribution to the chemistry of alkaloids in the early years of its development was made by the French researchers Pierre Joseph Pelletier and Joseph Bienaimé Caventou, who discovered quinine (1820) and strychnine (1818). Several other alkaloids were discovered around that time, including xanthine (1817), atropine (1819), caffeine (1820), coniine (1827), nicotine (1828), colchicine (1833), sparteine (1851), and cocaine (1860).^[33] The development of the chemistry of alkaloids was accelerated by the emergence of spectroscopic and chromatographic methods in the 20th century, so that by 2008 more than 12,000 alkaloids had been identified.^[34]

The first complete synthesis of an alkaloid was achieved in 1886 by the German chemist Albert Ladenburg. He produced coniine by reacting 2-methylpyridine with acetaldehyde and reducing the resulting 2-propenyl pyridine with sodium.^{[35][36]}

Classifications

Compared with most other classes of natural compounds, alkaloids are characterized by a great structural diversity. There is no uniform classification.^[37] Initially, when knowledge of chemical structures was lacking, botanical classification of the source plants was relied on. This classification is now considered obsolete.^{[5][38]}

More recent classifications are based on similarity of the carbon skeleton (*e.g.*, indole-, isoquinoline-, and pyridine-like) or biochemical precursor (ornithine, lysine, tyrosine, tryptophan, etc.).^[5] However, they require compromises in borderline cases;^[37] for example, nicotine contains a pyridine fragment from nicotinamide and a pyrrolidine part from ornithine^[39] and therefore can be assigned to both classes.^[40]

Alkaloids are often divided into the following major groups:^[41]

1. "True alkaloids" contain nitrogen in the heterocycle and originate from amino acids.^[42] Their characteristic examples are atropine, nicotine, and morphine. This group also includes some alkaloids that besides the nitrogen heterocycle contain terpene (*e.g.*, evonine^[43]) or peptide fragments (*e.g.* ergotamine^[44]). The piperidine alkaloids coniine and coniceine may be regarded as true alkaloids (rather than pseudoalkaloids: see below)^[45] although they do not originate from amino acids.^[46]
2. "Protoalkaloids", which contain nitrogen (but not the nitrogen heterocycle) and also originate from amino acids.^[42] Examples include mescaline, adrenaline and ephedrine.
3. Polyamine alkaloids – derivatives of putrescine, spermidine, and spermine.
4. Peptide and cyclopeptide alkaloids.^[47]
5. Pseudoalkaloids – alkaloid-like compounds that do not originate from amino acids.^[48] This group includes terpene-like and steroid-like alkaloids,^[49] as well as purine-like alkaloids such as caffeine, theobromine, theacrine and theophylline.^[50] Some authors classify as pseudoalkaloids such compounds such as ephedrine and cathinone. Those originate from the amino acid phenylalanine, but acquire their nitrogen atom not from the amino acid but through transamination.^{[50][51]}

Some alkaloids do not have the carbon skeleton characteristic of their group. So, galanthamine and homoaporphines do not contain isoquinoline fragment, but are, in general, attributed to isoquinoline alkaloids.^[52]

Main classes of monomeric alkaloids are listed in the table below:

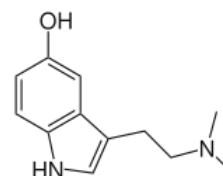
II. Ueber ein neues Pflanzenalkali
(Alkaloid).
Von
Dr. W. Meißner.

Die Reihe leicht zeretzbarer Pflanzenalkale, zu welcher das Morphium aus dem Weg gehoben hat, scheint sich mit jedem bekannten Schritt der Pflanzenanalyse zu vermehren, wie dies auch neuerlich die Aufklärung des Strychnin in der falsch St. Ignazi und aus venen durch Pelletier und Caventou bewies. Zu den schon bekannten kann ich nun noch ein neues hinzusetzen, welches ich zu Anfang dieses Jahres in dem Schöllkraute fand, und nicht ohne Schwierigkeiten für einen eigenthümlichen alkalischen Pflanzenkörper erkannte.

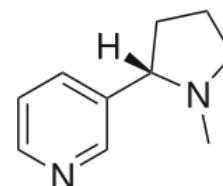
Man erhält ihn, indem man den Saamen mit mäßig starkem Alkohol ansetzt, diesen bei gelinder Wärme verdampft, oder aus einer Retorte abdestillirt, den harrigen Rückstand mit Wasser behandelt, die braune Auflösung filtrirt, und solange mit kohlensäurehaltigem Wasser versetzt, als noch die geringste Trübung entsteht, den Niederschlag so oft mit Wasser auswäscht, bis dieser ungelöst abfließt, und in gelinder Wärme trocknet.

Der auf diese Art erhaltene Stoff besitzt eine etwas schmutzig weiße Farbe; seinen bemerklichen Geruch, einen sehr bitteren Geschmack, wofür man auch eine sehr unangenehme lösende Einwirkung im Schlunde bemerkt, die auch entsteht, wenn man kaum


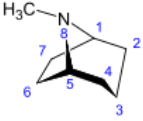

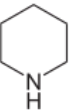
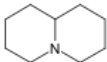
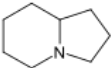

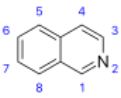
The article that introduced the concept of "alkaloid".




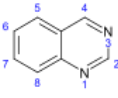
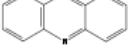
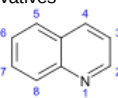
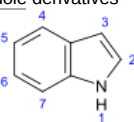



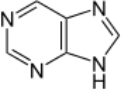
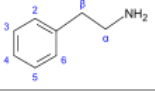
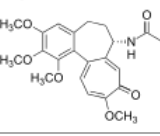
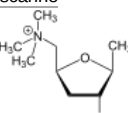
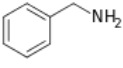




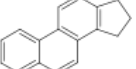
Bufotenin, an alkaloid from some toads, contains an indole core, and is produced in living organisms from the amino acid tryptophan.



The nicotine molecule contains both pyridine (left) and pyrrolidine rings (right).

Class	Major groups	Main synthesis steps	Examples
<i>Alkaloids with nitrogen heterocycles (true alkaloids)</i>			
Pyrrolidine derivatives ^[53] 		Ornithine or arginine → putrescine → N-methylputrescine → N-methyl-Δ ¹ -pyrroline ^[54]	Cuscohygrine, hygrine, hygroline, stachydrine ^{[53][55]}
Tropane derivatives ^[56] 	Atropine group Substitution in positions 3, 6 or 7	Ornithine or arginine → putrescine → N-methylputrescine → N-methyl-Δ ¹ -pyrroline ^[54]	Atropine, scopolamine, hyoscyamine ^{[53][56][57]}
	Cocaine group Substitution in positions 2 and 3		Cocaine, ecgonine ^{[56][58]}
Pyrrolizidine derivatives ^[59] 	Non-esters	In plants: ornithine or arginine → putrescine → homospermidine → retronecine ^[54] In fungi: L-proline + L-homoserine → N-(3-amino-3-carboxypropyl)proline → norloline ^{[61][62]}	Retronecine, heliotridine, laburnine ^{[59][60]}
	Complex esters of monocarboxylic acids		Indicine, lindelophin, sarracine ^[59]
	Macrocyclic diesters		Platyphylline, trichodesmine ^[59]
	1-aminopyrrolizidines (lolines)		Loline, N-formylloline, N-acetylloline ^[63]
Piperidine derivatives ^[64] 		Lysine → cadaverine → Δ ¹ -piperideine ^[65]	Sedamine, lobeline, anaferine, piperine ^{[45][66]}
		Octanoic acid → coniceine → coniine ^[46]	Coniine, coniceine ^[46]
Quinolizidine derivatives ^{[67][68]} 	Lupinine group	Lysine → cadaverine → Δ ¹ -piperideine ^[69]	Lupinine, nupharidin ^[67]
	Cytisine group		Cytisine ^[67]
	Sparteine group		Sparteine, lupanine, anahygrine ^[67]
	Matrine group.		Matrine, oxymatrine, allomatridine ^{[67][70][71]}
	Ormosanine group		Ormosanine, piptantine ^{[67][72]}
Indolizidine derivatives ^[73] 		Lysine → δ-semialdehyde of α-amino adipic acid → pipecolic acid → 1 indolizidinone ^[74]	Swainsonine, castanospermine ^[75]
Pyridine derivatives ^{[76][77]} 	Simple derivatives of pyridine	Nicotinic acid → dihydronicotinic acid → 1,2-dihydropyridine ^[78] Nicotinic acid, isoleucine ^[20]	Trigonelline, ricinine, arecoline ^{[76][79]}
	Polycyclic noncondensing pyridine derivatives		Nicotine, normicotine, anabasine, anatabine ^{[76][79]}
	Polycyclic condensed pyridine derivatives		Actinidine, gentianine, pedicularine ^[80]
	Sesquiterpene pyridine derivatives		Evonine, hippocrateine, triptonine ^{[77][78]}
Isoquinoline derivatives and related alkaloids ^[81] 	Simple derivatives of isoquinoline ^[82]	Tyrosine or phenylalanine → dopamine or tyramine (for alkaloids Amarillis) ^{[83][84]}	Salsoline, lophocerin ^{[81][82]}
	Derivatives of 1- and 3-isoquinolines ^[85]		N-methylcoridaline, noroxyhydrastinine ^[85]
	Derivatives of 1- and 4-phenyltetrahydroisoquinolines ^[82]		Cryptostilin ^{[82][86]}
	Derivatives of 5-naftil-isoquinoline ^[87]		Ancistrocladine ^[87]
	Derivatives of 1- and 2-benzyl-isoquinolines ^[88]		Papaverine, laudanose, sendaverine
	Cularine group ^[89]		Cularine, yagonine ^[89]
	Pavines and isopavines ^[90]		Argemonine, amurensine ^[90]
	Benzopyrrocolines ^[91]		Cryptaustoline ^[82]
	Protoberberines ^[82]		Berberine, canadine, ophiocarpine, mecambidine, corydaline ^[92]
	Phthalidisoquinolines ^[82]		Hydrastine, narcotine (Noscapine) ^[93]
	Spirobenzylisoquinolines ^[82]		Fumaricine ^[90]
	Ipecacuanha alkaloids ^[94]		Emetine, protoemetine, ipecoside ^[94]
	Benzophenanthridines ^[82]		Sanguinarine, oxynitidine, corynoloxine ^[95]
	Aporphines ^[82]		Glauicine, coridine, liriodenine ^[96]

	Proaporphines [82]		Pronuciferine, glaziovine [82][91]	
	Homoaporphines [97]		Kreysiginine, multifloramine [97]	
	Homoproaporphines [97]		Bulbocodine [89]	
	Morphines [98]		Morphine, codeine, thebaine, sinomenine [99]	
	Homomorphines [100]		Kreysiginine, androcymbine [98]	
	Tropoloisoquinolines [82]		Imerubrine [82]	
	Azofluoranthenes [82]		Rufescine, imeluteine [101]	
	Amaryllis alkaloids [102]		Lycorine, ambelline, tazettine, galantamine, montanine [103]	
	Erythrina alkaloids [86]		Erysodine, erythroidine [86]	
	Phenanthrene derivatives [82]		Atherosperminine [82][92]	
	Protopines [82]		Protopine, oxomuramine, corycavidine [95]	
	Aristolactam [82]		Doriflavin [82]	
Oxazole derivatives [104]		Tyrosine → tyramine [105]	Annuloline, halfordinol, texaline, texamine [106]	
Isoxazole derivatives		Ibotenic acid → Muscimol	Ibotenic acid, Muscimol	
Thiazole derivatives [107]		1-Deoxy-D-xylulose 5-phosphate (DOXP), tyrosine, cysteine [108]	Nostocyclamide, thiostreptone [107][109]	
Quinazoline derivatives [110]		3,4-Dihydro-4-quinazoline derivatives	Febrifugine [112]	
		1,4-Dihydro-4-quinazoline derivatives	Glycorine, arborine, glycosminine [112]	
		Pyrrolidine and piperidine quinazoline derivatives	Vazicine (peganine) [104]	
Acridine derivatives [104]		Anthranilic acid [113]	Rutacridone, acronicine [114][115]	
Quinoline derivatives [116][117]		Simple derivatives of quinoline derivatives of 2-quinolones and 4-quinolone	Cusparine, echinopsine, evocarpine [117][119][120]	
		Tricyclic terpenoids	Flindersine [117][121]	
		Furanoquinoline derivatives	Dictamnine, fagarine, skimmianine [117][122][123]	
		Quinines	Quinine, quinidine, cinchonine, cinchonidine [121]	
Indole derivatives [99]		<i>Non-isoprene indole alkaloids</i>		
		Simple indole derivatives [124]	Serotonin, psilocybin, dimethyltryptamine (DMT), bufotenin [126][127]	
		Simple derivatives of β-carboline [128]	Harman, harmine, harmaline, eleagnine [124]	
		Pyrroloindole alkaloids [129]	Physostigmine (eserine), etheramine, physovenine, eptastigmine [129]	
		<i>Semiterpenoid indole alkaloids</i>		
		Ergot alkaloids [99]	Tryptophan → chanoclavine → agroclavine → elimoclavine → paspalic acid → lysergic acid [129]	Ergotamine, ergobasine, ergosine [130]
		<i>Monoterpenoid indole alkaloids</i>		
Corynanthe type alkaloids [125]	Tryptophan → tryptamine → strictosidine (with secologanin) [125]	Ajmalicine, sarpagine, vobasine, ajmaline, yohimbine, reserpine, mitragynine, [131][132] group strychnine and (Strychnine brucine, aquamicine, vomicine [133])		
Iboga-type alkaloids [125]		Ibogamine, ibogaine, voacangine [125]		

	Aspidosperma-type alkaloids ^[125]		Vincamine, <i>vinca</i> alkaloids, ^{[26][134]} vincotine, aspidospermine ^{[135][136]}
Imidazole derivatives ^[104] 		Directly from histidine ^[137]	Histamine, pilocarpine, pilosine, stevensine ^{[104][137]}
Purine derivatives ^[138] 		Xanthosine (formed in purine biosynthesis) → 7-methylxanthosine → 7-methyl xanthine → theobromine → caffeine ^[84]	Caffeine, theobromine, theophylline, saxitoxin ^{[139][140]}
<i>Alkaloids with nitrogen in the side chain (protoalkaloids)</i>			
β -Phenylethylamine derivatives ^[91] 		Tyrosine or phenylalanine → dioxyphenilalanine → dopamine → adrenaline and mescaline tyrosine → tyramine phenylalanine → 1-phenylpropane-1,2-dione → cathinone → ephedrine and pseudoephedrine ^{[20][51][141]}	Tyramine, ephedrine, pseudoephedrine, mescaline, cathinone, catecholamines (adrenaline, noradrenaline, dopamine) ^{[20][142]}
Colchicine alkaloids ^[143] 		Tyrosine or phenylalanine → dopamine → autumnaline → colchicine ^[144]	Colchicine, colchamine ^[143]
Muscarine ^[145] 		Glutamic acid → 3-ketoglutamic acid → muscarine (with pyruvic acid) ^[146]	Muscarine, allomuscarine, epimuscarine, epiallomuscarine ^[145]
Benzylamine ^[147] 		Phenylalanine with valine, leucine or isoleucine ^[148]	Capsaicin, dihydrocapsaicin, nordihydrocapsaicin, vanillylamine ^{[147][149]}
<i>Polyamines alkaloids</i>			
Putrescine derivatives ^[150] 		ornithine → putrescine → spermidine → spermine ^[151]	Paucine ^[150]
Spermidine derivatives ^[150] 			Lunarine, codonocarpine ^[150]
Spermine derivatives ^[150] 			Verbascenine, aphelandrine ^[150]
<i>Peptide (cyclopeptide) alkaloids</i>			
Peptide alkaloids with a 13-membered cycle ^{[47][152]}	Nummularine C type	From different amino acids ^[47]	Nummularine C, Nummularine S ^[47]
	Ziziphine type		Ziziphine A, sativanine H ^[47]
Peptide alkaloids with a 14-membered cycle ^{[47][152]}	Frangulanine type		Frangulanine, scutianine J ^[152]
	Scutianine A type		Scutianine A ^[47]
	Integerrine type		Integerrine, discarine D ^[152]
	Amphibine F type		Amphibine F, spinanine A ^[47]
	Amfibine B type		Amphibine B, lotusine C ^[47]
Peptide alkaloids with a 15-membered cycle ^[152]	Mucronine A type		Mucronine A ^{[44][152]}
<i>Pseudoalkaloids (terpenes and steroids)</i>			
Diterpenes ^[44] 	Lycotoxine type	Mevalonic acid → Isopentenyl pyrophosphate → geranyl pyrophosphate ^{[153][154]}	Aconitine, delphinine ^{[44][155]}
Steroids ^[156] 		Cholesterol, arginine ^[157]	Solasodine, solanidine, veralkamine, batrachotoxin ^[158]

Properties

Most alkaloids contain oxygen in their molecular structure; those compounds are usually colorless crystals at ambient conditions. Oxygen-free alkaloids, such as nicotine^[159] or coniine,^[35] are typically volatile, colorless, oily liquids.^[160] Some alkaloids are colored, like berberine (yellow) and sanguinarine (orange).^[160]

Most alkaloids are weak bases, but some, such as theobromine and theophylline, are amphoteric.^[161] Many alkaloids dissolve poorly in water but readily dissolve in organic solvents, such as diethyl ether, chloroform or 1,2-dichloroethane. Caffeine,^[162] cocaine,^[163] codeine^[164] and nicotine^[165] are slightly soluble in water (with a solubility of $\geq 1\text{g/L}$), whereas others, including morphine^[166] and yohimbine^[167] are very slightly water-soluble (0.1–1 g/L). Alkaloids and acids form salts of various strengths. These salts are usually freely soluble in water and ethanol and poorly soluble in most organic solvents. Exceptions include scopolamine hydrobromide, which is soluble in organic solvents, and the water-soluble quinine sulfate.^[160]

Most alkaloids have a bitter taste or are poisonous when ingested. Alkaloid production in plants appeared to have evolved in response to feeding by herbivorous animals; however, some animals have evolved the ability to detoxify alkaloids.^[168] Some alkaloids can produce developmental defects in the offspring of animals that consume but cannot detoxify the alkaloids. One example is the alkaloid cycloamine, produced in the leaves of corn lily. During the 1950s, up to 25% of lambs born by sheep that had grazed on corn lily had serious facial deformations. These ranged from deformed jaws to cyclopia (see picture). After decades of research, in the 1980s, the compound responsible for these deformities was identified as the alkaloid 11-deoxyjervine, later renamed to cyclopamine.^[169]



Head of a calf born to a cow that ate leaves of the corn lily plant. The cyclopia in the calf is induced by the alkaloid cyclopamine present in the plant.

Distribution in nature

Alkaloids are generated by various living organisms, especially by higher plants – about 10 to 25% of those contain alkaloids.^{[170][171]} Therefore, in the past the term "alkaloid" was associated with plants.^[172]

The alkaloids content in plants is usually within a few percent and is inhomogeneous over the plant tissues. Depending on the type of plants, the maximum concentration is observed in the leaves (black henbane), fruits or seeds (Strychnine tree), root (Rauvolfia serpentina) or bark (cinchona).^[173] Furthermore, different tissues of the same plants may contain different alkaloids.^[174]

Beside plants, alkaloids are found in certain types of fungi, such as psilocybin in the fungus of the genus Psilocybe, and in animals, such as bufotenin in the skin of some toads^[23] and a number of insects, markedly ants.^[175] Many marine organisms also contain alkaloids.^[176] Some amines, such as adrenaline and serotonin, which play an important role in higher animals, are similar to alkaloids in their structure and biosynthesis and are sometimes called alkaloids.^[177]



Strychnine tree. Its seeds are rich in strychnine and brucine.

Extraction

Because of the structural diversity of alkaloids, there is no single method of their extraction from natural raw materials.^[178] Most methods exploit the property of most alkaloids to be soluble in organic solvents^[7] but not in water, and the opposite tendency of their salts.

Most plants contain several alkaloids. Their mixture is extracted first and then individual alkaloids are separated.^[179] Plants are thoroughly ground before extraction.^{[178][180]} Most alkaloids are present in the raw plants in the form of salts of organic acids.^[178] The extracted alkaloids may remain salts or change into bases.^[179] Base extraction is achieved by processing the raw material with alkaline solutions and extracting the alkaloid bases with organic solvents, such as 1,2-dichloroethane, chloroform, diethyl ether or benzene. Then, the impurities are dissolved by weak acids; this converts alkaloid bases into salts that are washed away with water. If necessary, an aqueous solution of alkaloid salts is again made alkaline and treated with an organic solvent. The process is repeated until the desired purity is achieved.

In the acidic extraction, the raw plant material is processed by a weak acidic solution (*e.g.*, acetic acid in water, ethanol, or methanol). A base is then added to convert alkaloids to basic forms that are extracted with organic solvent (if the extraction was performed with alcohol, it is removed first, and the remainder is dissolved in water). The solution is purified as described above.^{[178][181]}

Alkaloids are separated from their mixture using their different solubility in certain solvents and different reactivity with certain reagents or by distillation.^[182]

A number of alkaloids are identified from insects, among which the fire ant venom alkaloids known as solenopsins have received greater attention from researchers.^[183] These insect alkaloids can be efficiently extracted by solvent immersion of live fire ants^[7] or by centrifugation of live ants^[184] followed by silica-gel chromatography purification.^[185] Tracking and dosing the extracted solenopsin ant alkaloids has been described as possible based on their absorbance peak around 232 nanometers.^[186]



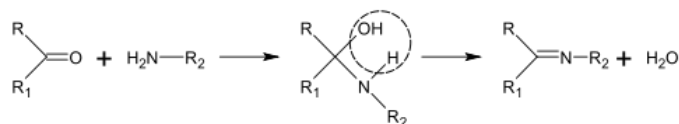
Crystals of piperine extracted from black pepper.

Biosynthesis

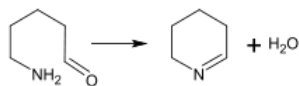
Biological precursors of most alkaloids are amino acids, such as ornithine, lysine, phenylalanine, tyrosine, tryptophan, histidine, aspartic acid, and anthranilic acid.^[187] Nicotinic acid can be synthesized from tryptophan or aspartic acid. Ways of alkaloid biosynthesis are too numerous and cannot be easily classified.^[84] However, there are a few typical reactions involved in the biosynthesis of various classes of alkaloids, including synthesis of Schiff bases and Mannich reaction.^[187]

Synthesis of Schiff bases

Schiff bases can be obtained by reacting amines with ketones or aldehydes.^[188] These reactions are a common method of producing C=N bonds.^[189]

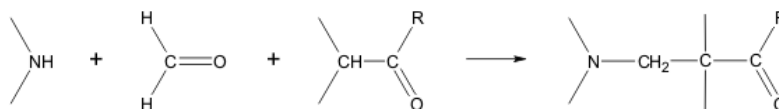


In the biosynthesis of alkaloids, such reactions may take place within a molecule,^[187] such as in the synthesis of piperidine:^[40]

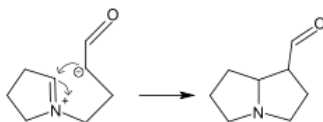


Mannich reaction

An integral component of the Mannich reaction, in addition to an amine and a carbonyl compound, is a carbanion, which plays the role of the nucleophile in the nucleophilic addition to the ion formed by the reaction of the amine and the carbonyl.^[189]



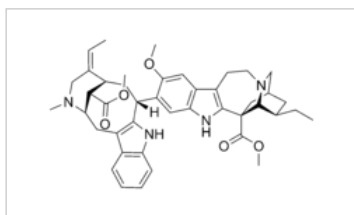
The Mannich reaction can proceed both intermolecularly and intramolecularly:^{[190][191]}



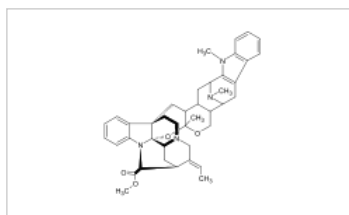
Dimer alkaloids

In addition to the described above monomeric alkaloids, there are also dimeric, and even trimeric and tetrameric alkaloids formed upon condensation of two, three, and four monomeric alkaloids. Dimeric alkaloids are usually formed from monomers of the same type through the following mechanisms:^[192]

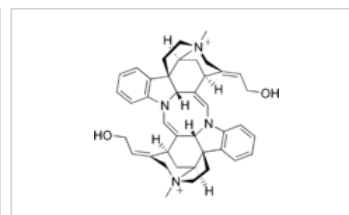
- Mannich reaction, resulting in, e.g., voacamine
- Michael reaction (villalstonine)
- Condensation of aldehydes with amines (toxiferine)
- Oxidative addition of phenols (dauricine, tubocurarine)
- Lactonization (carpaine).



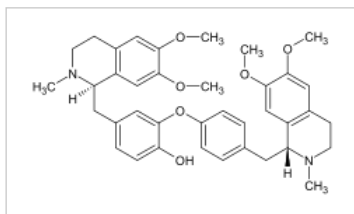
Voacamine



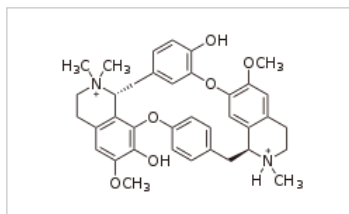
Villalstonine



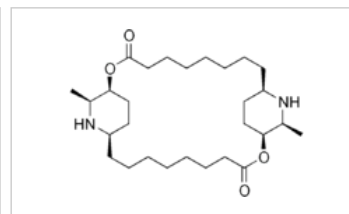
Toxiferine



Dauricine

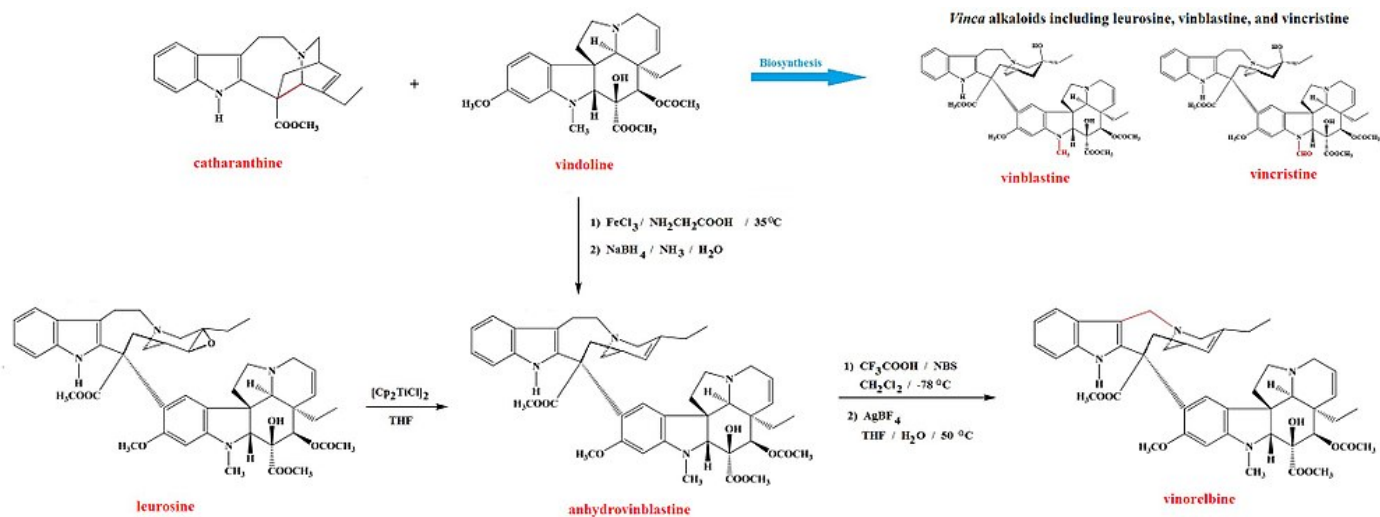


Tubocurarine



Carpaine

There are also dimeric alkaloids formed from two distinct monomers, such as the *vinca* alkaloids vinblastine and vincristine,^{[26][134]} which are formed from the coupling of catharanthine and vindoline.^{[193][194]} The newer semi-synthetic chemotherapeutic agent vinorelbine is used in the treatment of non-small-cell lung cancer.^{[134][195]} It is another derivative dimer of vindoline and catharanthine and is synthesised from anhydrovinblastine,^[196] starting either from leurosine^{[197][198]} or the monomers themselves.^{[134][194]}



Biological role

The role of alkaloids for living organisms that produce them is still unclear.^[199] It was initially assumed that the alkaloids are the final products of nitrogen metabolism in plants, as urea in mammals. It was later shown that alkaloid concentration varies over time, and this hypothesis was refuted.^[16] A number of ants are suggested to also produce alkaloids as venom components, however the exact biosynthesis pathways have not been empirically demonstrated.^{[175][200]}

Most of the known functions of alkaloids are related to protection. For example, aporphine alkaloid liriodenine produced by the tulip tree protects it from parasitic mushrooms. In addition, the presence of alkaloids in the plant prevents insects and chordate animals from eating it. However, some animals are adapted to alkaloids and even use them in their own metabolism.^[201] Such alkaloid-related substances as serotonin, dopamine and histamine are important neurotransmitters in animals. Alkaloids are also known to regulate plant growth.^[202] One example of an organism that uses alkaloids for protection is the Utetheisa ornatrix, more commonly known as the ornate moth. Pyrrolizidine alkaloids render these larvae and adult moths unpalatable to many of their natural enemies like coccinellid beetles, green lacewings, insectivorous hemiptera and insectivorous bats.^[203] Another example of alkaloids being utilized occurs in the poison hemlock moth (Agonopterix astroemeriana). This moth feeds on its highly toxic and alkaloid-rich host plant poison hemlock (Conium maculatum) during its larval stage. A. astroemeriana may benefit twofold from the toxicity of the naturally-occurring alkaloids, both through the unpalatability of the species to predators and through the ability of A. astroemeriana to recognize Conium maculatum as the correct location for oviposition.^[204] A fire ant venom alkaloid known as solenopsin has been demonstrated to protect queens of invasive fire ants during the foundation of new nests, thus playing a central role in the spread of this pest ant species around the world.^[205]

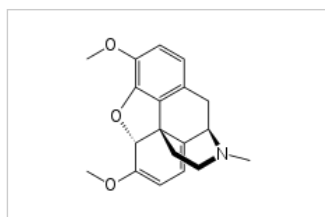
Applications

In medicine

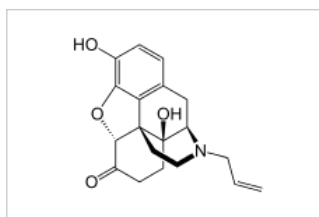
Medical use of alkaloid-containing plants has a long history, and, thus, when the first alkaloids were isolated in the 19th century, they immediately found application in clinical practice.^[206] Many alkaloids are still used in medicine, usually in the form of salts widely used including the following:^{[16][207]}

Alkaloid	Action
<u>Ajmaline</u>	<u>antiarrhythmic</u>
<u>Atropine, scopolamine, hyoscyamine</u>	<u>anticholinergic</u>
<u>Caffeine</u>	<u>stimulant, adenosine receptor antagonist</u>
<u>Codeine</u>	<u>antitussive, analgesic</u>
<u>Colchicine</u>	<u>remedy for gout</u>
<u>Emetine</u>	<u>antiprotozoal agent,</u> <u>Emesis</u>
<u>Ergot alkaloids</u>	<u>Vasoconstriction, hallucinogenic, Uterotonic</u>
<u>Morphine</u>	<u>analgesic</u>
<u>Nicotine</u>	<u>stimulant, nicotinic acetylcholine receptor agonist</u>
<u>Physostigmine</u>	<u>inhibitor of acetylcholinesterase</u>
<u>Quinidine</u>	<u>antiarrhythmic</u>
<u>Quinine</u>	<u>antipyretic, antimalarial</u>
<u>Reserpine</u>	<u>antihypertensive</u>
<u>Tubocurarine</u>	<u>muscle relaxant</u>
<u>Vinblastine, vincristine</u>	<u>antitumor</u>
<u>Vincamine</u>	<u>vasodilating, antihypertensive</u>
<u>Yohimbine</u>	<u>stimulant, aphrodisiac</u>

Many synthetic and semisynthetic drugs are structural modifications of the alkaloids, which were designed to enhance or change the primary effect of the drug and reduce unwanted side-effects.^[208] For example, naloxone, an opioid receptor antagonist, is a derivative of thebaine that is present in opium.^[209]



Thebaine



Naloxone

In agriculture

Prior to the development of a wide range of relatively low-toxic synthetic pesticides, some alkaloids, such as salts of nicotine and anabesine, were used as insecticides. Their use was limited by their high toxicity to humans.^[210]

Use as psychoactive drugs

Preparations of plants containing alkaloids and their extracts, and later pure alkaloids, have long been used as psychoactive substances. Cocaine, caffeine, and cathinone are stimulants of the central nervous system.^{[211][212]} Mescaline and many indole alkaloids (such as psilocybin, dimethyltryptamine and ibogaine) have hallucinogenic effect.^{[213][214]} Morphine and codeine are strong narcotic pain killers.^[215]

There are alkaloids that do not have strong psychoactive effect themselves, but are precursors for semi-synthetic psychoactive drugs. For example, ephedrine and pseudoephedrine are used to produce methcathinone and methamphetamine.^[216] Thebaine is used in the synthesis of many painkillers such as oxycodone.

See also

- Amine
- Base (chemistry)
- List of poisonous plants
- Natural products
- Palau'amine
- Secondary metabolite
- Mayer's reagent

Notes

1. In the penultimate sentence of his article, W. Meissner (1819) "Über Pflanzenalkalien: II. Über ein neues Pflanzenalkali (Alkaloid)" (On plant alkalis: II. On a new plant alkali (alkaloid)), *Journal für Chemie und Physik*, **25** : 379–381 ; available on-line at: Hathi Trust (<http://babel.hathitrust.org/cgi/pt?id=nyp.33433069069056;view=1up;seq=415>) – Meissner wrote: "Überhaupt scheint es mir auch angemessen, die bis jetzt bekannten Pflanzenstoffe nicht mit dem Namen Alkalien, sondern Alkaloide zu belegen, da sie doch in manchen Eigenschaften von den Alkalien sehr abweichen, sie würden daher in dem Abschnitt der Pflanzenchemie vor den Pflanzensäuren ihre Stelle finden." (1.

49. Plemenkov, p. 246
50. Aniszewski, p. 12
51. Dewick, p. 382
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53. Plemenkov, p. 224
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58. Aniszewski, p. 27
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65. Aniszewski, p. 95
66. Orekhov, p. 80
67. Chemical Encyclopedia: Quinolizidine alkaloids (<http://www.xumuk.ru/encyklopedia/2/5011.html>). xumuk.ru
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69. Aniszewski, p. 98
70. Saxton, Vol. 1, p. 91
71. Joseph P. Michael (2002). "Indolizidine and quinolizidine alkaloids". *Nat. Prod. Rep.* **19** (5): 458–475. doi:10.1039/b208137g (<https://doi.org/10.1039/b208137g>). PMID 14620842 (<https://pubmed.ncbi.nlm.nih.gov/14620842>).
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73. Dewick, p. 310
74. Aniszewski, p. 96
75. Aniszewski, p. 97
76. Plemenkov, p. 227
77. Chemical Encyclopedia: pyridine alkaloids (<http://www.xumuk.ru/encyklopedia/2/3336.html>). xumuk.ru
78. Aniszewski, p. 107
79. Aniszewski, p. 85
80. Plemenkov, p. 228
81. Hesse, p. 36
82. Chemical Encyclopedia: isoquinoline alkaloids (<http://www.xumuk.ru/encyklopedia/1642.html>). xumuk.ru
83. Aniszewski, pp. 77–78
84. Begley, Alkaloid Biosynthesis
85. Saxton, Vol. 3, p. 122
86. Hesse, p. 54
87. Hesse, p. 37
88. Hesse, p. 38
89. Hesse, p. 46
90. Hesse, p. 50
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93. Hesse, p. 39
94. Hesse, p. 41
95. Hesse, p. 49
96. Hesse, p. 44
97. Saxton, Vol. 3, p. 164
98. Hesse, p. 51
99. Plemenkov, p. 236
100. Saxton, Vol. 3, p. 163
101. Saxton, Vol. 3, p. 168
102. Hesse, p. 52
103. Hesse, p. 53
104. Plemenkov, p. 241
105. Brossi, Vol. 35, p. 261
106. Brossi, Vol. 35, pp. 260–263
107. Plemenkov, p. 242
108. Begley, Cofactor Biosynthesis
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115. Hesse, p. 58
116. Plemenkov, p. 231
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120. Hesse, p. 55
121. Plemenkov, p. 232
122. Orekhov, p. 212
123. Aniszewski, p. 118
124. Aniszewski, p. 112
125. Aniszewski, p. 113
126. Hesse, p. 15
127. Saxton, Vol. 1, p. 467
128. Dewick, pp. 349–350
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137. Aniszewski, p. 104

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71. Orekhov, p. 11
72. Hesse, p.4
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